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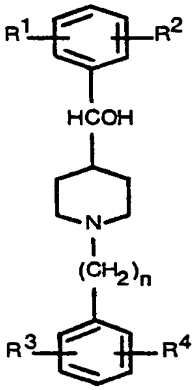
Description

This invention relates to a new class of compounds having important biochemical and pharmacological properties. More particularly, this invention relates to N-aralkyl piperidinemethanol derivatives which are potent and selective inhibitors of the binding of serotonin at the $5HT_2$ receptor site, and to the processes for their preparation and use.

The compounds of this invention are represented by the general formula I



I

including optical isomers and mixtures thereof, the pharmaceutically acceptable salts thereof, wherein n is 2, 3 or 4 and each of R^1, R^2, R^3 and R^4 independently represents hydrogen, C_{1-6} alkyl, halogen, trifluoromethyl, hydroxy, C_{1-6} alkoxy or amino.

Representative of the R^1 to R^4 substituents for C_{1-6} alkyl are methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, pentyl, hexyl, cyclopropyl, cyclopentyl with methyl and ethyl being preferred. All halogens are embraced with fluoro and chloro being preferred. Representative C_{1-6} alkoxy substituents are methoxy, ethoxy, isopropoxy and such of the aforementioned alkyl groups attached thru an oxygen. In those instances wherein R^1 to R^4 are other than hydrogen, the substituents may be located at any position, (ortho, meta or para) but para is preferred for monosubstituted phenyl moieties. The 2,3-, 2,4-, 2,5-, 3,4-, or 3,5-disubstituted phenyl moieties are embraced herein. The compounds of Formula I contain an asymmetric carbon atom and thus exist in optically isomeric forms. Embraced within this invention are the individual optical isomers and the mixtures thereof. Such mixtures may readily be separated by standard techniques well known in the art.

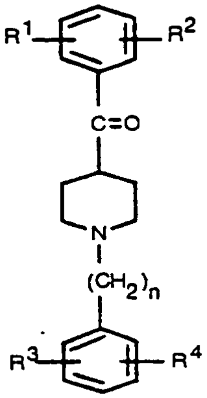
Preferred are the following compounds of the general formula (I):

The compounds wherein n is 2; the compounds wherein n is 3; the compounds wherein R^3 and R^4 are hydrogen; the compounds wherein R^1 to R^4 are hydrogen; the compounds wherein R^1 and R^2 are methoxy and R^3 and R^4 are hydrogen; the compounds wherein R^1 is methoxy and each of R^2, R^3 and R^4 is hydrogen; the compounds wherein R^1 and R^2 are halogen and R^3 and R^4 are hydrogen; and the compounds wherein R^1 is methyl and R^2, R^3 and R^4 are hydrogen.

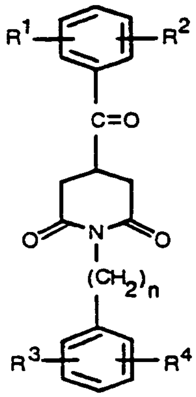
The preparation of the compounds of this invention may be achieved by standard chemical reactions analogously known in the art.

The compounds of the general formula I may be prepared by one of the following processes:

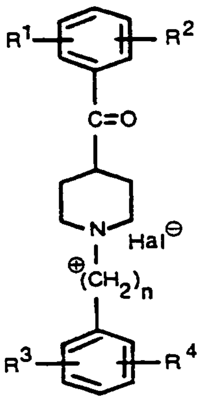
A) the chemical reduction of compounds of the formulae II



IIa

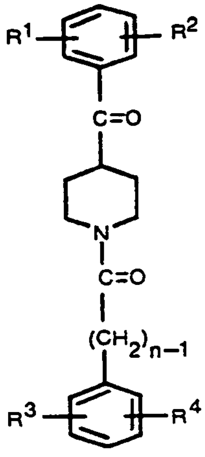


IIb



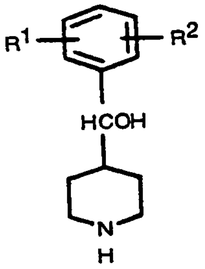
IIc

or



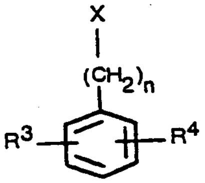
IId

B) the alkylation of a compound of the formula III



III

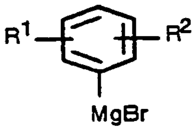
with a reactive derivative having the formula IV



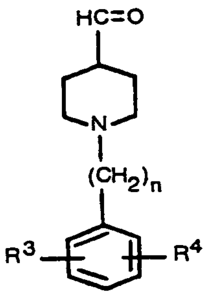
IV

wherein X is a reactive moiety, preferably a halide, tosylate, mesylate or a functional equivalent thereof, or

C) the reaction of a Grignard reagent V with an aldehyde of the formula VI



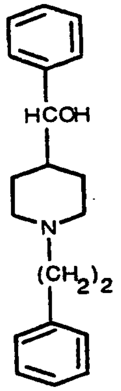
V



VI

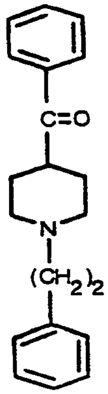
and hydrolyzing the reaction product,
wherein R^1 to R^4 and n is defined as above.

Especially preferred is the compound of formula VII

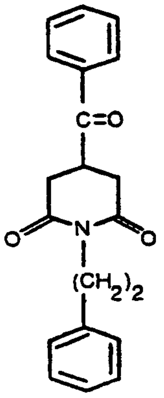


VII

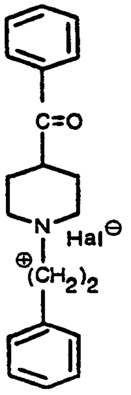
This compound can be obtained according to one of the following methods:
A) the chemical reduction of compounds of the formulae VIII



VIIIa

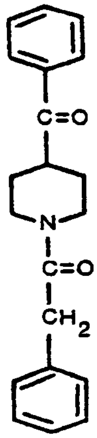


VIIIb



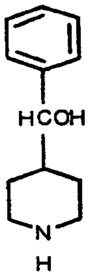
VIIIc

or



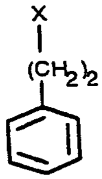
VIIId

B) the alkylation of the compound of formula IX



IX

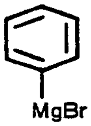
with an alkylating agent of the formula X



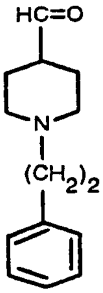
X

wherein the X-substituent is a halide, tosylate, mesylate or a functional equivalent thereof, or

C) the reaction of a Grignard reagent XI with an aldehyde of the formula XII



XI

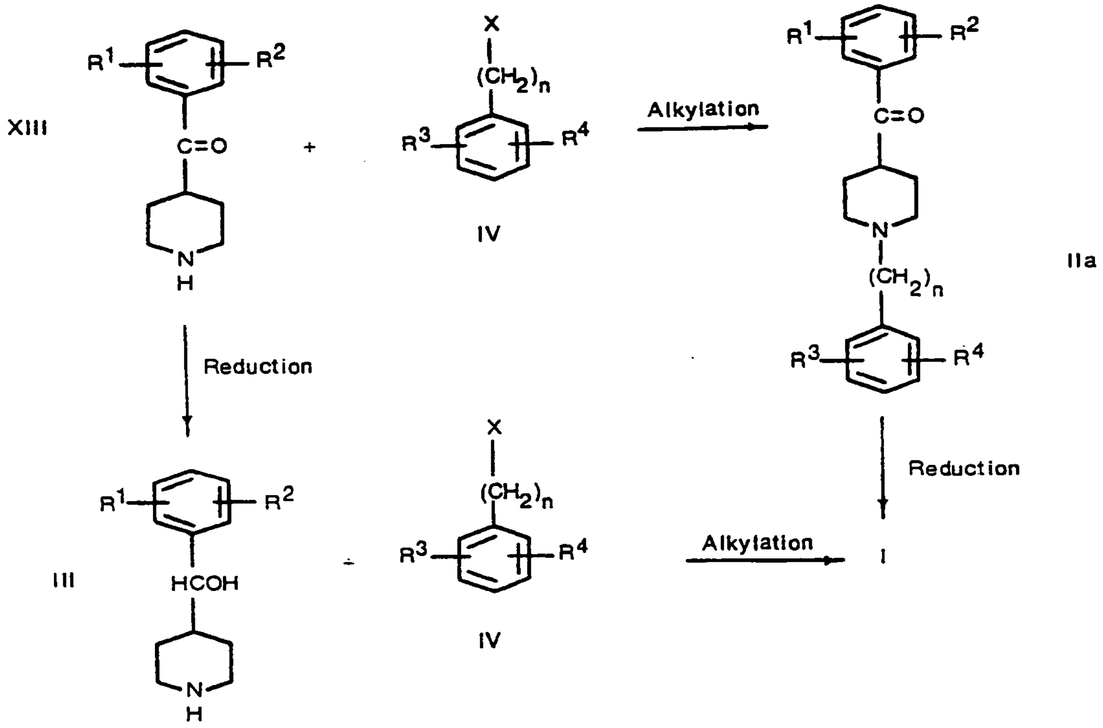


XII

and hydrolyzing the reaction product.

To obtain the compounds of formula IIa it is preferred to N-alkylate an appropriately R^1,R^2-substituted phenyl 4-piperidinemethanone (XIII) to produce an R^1,R^2 phenyl [1-R^3,R^4-phenylalkyl-4-piperidinyl] methanone intermediate (IIa), which is then chemically reduced to the desired product (I). Alternatively the 4-piperidinones (XIII) may be chemically reduced to their alcohols (III) and these intermediates may be N-alkylated to the desired products (I). The chemical reduction of the ketones to their corresponding alcohols may be effected by standard reduction procedures such as by catalytic hydrogenation or metal hydride reduction preferably with sodium or potassium borohydride. In either case in those instances wherein any R^1 to R^4 substituent represents a reactive hydroxy group then such group should first be protected (using such standard protecting groups as acetate, trifluoroacetate, benzyloxy, benzyloxycarbonyl and the like) and then, following the foregoing N-alkylation-reduction reactions, the protecting group is removed. Standard techniques for protecting and de-protecting hydroxy functions are well known in the art. Analogously in those instances wherein any R^1 to R^4 group represents an amino moiety, it is preferred to prepare the appropriate nitro analog and, as a last step, reduce the nitro group to the desired amino moiety. The foregoing reactions may conveniently be depicted by the following reaction scheme.

Reaction Scheme A



wherein X is a suitable leaving group (e.g., halide, tosylate or other functional equivalent thereof) and n, R^1, R^2, R^3 and R^4 are as defined for compounds of Formula I.

The N-alkylation procedures are effected by reacting about equimolar quantities of the N-alkylating reactants (IV) with an appropriately substituted 4-piperidine-methanol (III) or 4-piperidinylmethanone (XIII), in a suitable solvent, in the presence of an acid acceptor (e.g., the carbonates or bicarbonates of potassium or sodium, or an excess of the piperidine reactant), optionally with a small amount of potassium iodide being present. Suitable solvents are toluene, xylene, chlorobenzene, N,N-dimethylformamide, N,N-dimethylacetamide, ketones (acetone, butanone, MIBK, cyclohexanone, cyclopentanone, etc.) and alcohols (ethanol, propanol, butanol, etc). The reaction mixture is heated over a wide range of temperatures (50°C—180°C) although it is preferred to heat at reflux temperatures of the reaction mixture. The reaction is continued until completed, generally a period of several hours to several days.

After completion of the reaction, the reaction mixture is filtered, the product optionally converted to its mineral or organic acid salt and the desired product is recrystallized by techniques well-known in the art. Suitable solvents for recrystallization are methanol, ethanol, isopropanol, butanone, acetone, ethyl acetate, diethylether and the like.

The intermediate R^1,R^2-substituted phenyl 4-piperidyl-ketones (XIII) used in the preparation of the compounds of Reaction Scheme A may be prepared by a Friedel-Craft reaction of benzene or a R^1,R^2-substituted benzene with isonipecotic acid chloride HCl or N-trifluoroacetyl isonipecotic trifluoroacetic anhydride followed by aqueous potassium carbonate hydrolysis in the latter case. Reaction of a substituted phenyl Grignard reagent with 4-cyanopiperidine (prepared by hydrolyzing N-trifluoroacetyl-4-cyanopiperidine) will also yield the intermediate ketones.

Alternative methods of synthesis of the compounds of this invention include the reactions of either a R^1,R^2-phenylmagnesium halide (V) or a R^1,R^2-substituted phenyl lithium reactant with 1-(ω-R^3,R^4-phenyl alkyl)-4-piperidine carboxaldehyde (VI). Another alternative procedure includes the catalytic hydrogenation of an alpha-(R^1,R^2, phenyl-methanol)-1-(R^3,R^4-phenylalkyl)pyridinium halide, or its ketone analog (IIc), to the desired product. Still another method is the chemical reduction of a R^1,R^2-phenyl[-1(2-R^3, R^4-phenacyl)-4-piperidinyl]-methanone (IId) to the desired products of this invention. For these foregoing reactions standard procedures well known in the art may be used in the preparation of the necessary intermediates as well as for the final step producing the desired products.

Having taught the general methods for the preparation of the compounds of this invention the following examples typify the preferred routes of preparation.

Example 1

Alpha-phenyl-1-(2-phenylethyl)-4-piperidinemethanol HCl

Step A: Phenyl[1-(2-phenylethyl)-4-piperidinyl]-methanone HCl. A reaction mixture containing phenyl(4-piperidinyl)methanone (20.5 g, 0.108 mol; K_2CO_3 (33.17 g, 0.18 mol), potassium iodide (0.2 g) and 2-bromoethyl benzene (22.2 g, 0.12 mol, 16.4 ml) in toluene (250 ml) was stirred at reflux temperature for 66 h. The reaction mixture was filtered and the filtrate concentrated to a residue which was dissolved in dry Et_2O (500 ml) and treated dropwise with a solution of HCl (0.11 mol) in EtOAc. The resultant precipitate was recrystallized from $EtOHCH_3OH$, 4:1 (500 ml) to give phenyl[1-(2-phenylethyl)-4-piperidinylmethanone hydrochloride, mp 258—260°C.

Step B; A solution of phenyl[1-(2-phenylethyl)-4-piperidinyl]methanone (11.0 g, 0.037 mol) in absolute EtOH (150 ml) was stirred at room temperature and treated portionwise with $NaBH_4$ (2.84 g, 0.075 mol) and was stirred overnight (16 h). The reaction mixture was concentrated at reduced pressure to give a residue which was partitioned between CH_2Cl_2 (250 ml) and 10% NaOH solution (100 ml). The aqueous layer was further extracted with CH_2Cl_2 (2 × 50 ml) and the combined extracts washed with saturated NaCl solution (100 ml) and dried over $MgSO_4$. The mixture was filtered and concentrated to give a solid (10 g) which was dissolved in dry Et_2O/EtOAc (1:1, 350 ml) and treated with HCl (0.034 mol) dissolved in EtOAc/CH_3OH (3:1, 20 ml). The resultant precipitate was recrystallized twice from methanol/butanone to give phenyl-1-(2-phenylethyl)-4-piperidinemethanol hydrochloride, mp 141—143.5°C.

Example 2

Alpha-phenyl-1-(2-phenylethyl)-4-piperidinemethanol

A mixture of alpha-phenyl-4-piperidinemethanol (1.5 g, 7.8 mmol), 2-bromoethyl benzene (1.1 ml, 8.0 mmol) and potassium carbonate (1.1 g, 8.0 mmol) in dry DMF (20 ml) was heated at 80°C over the weekend (60 h). The excess DMF was distilled off at reduced pressure and the residue was dissolved in ethyl acetate. The organic phase was washed with H_2O (3 × 100 ml), saturated aqueous NaCl (1 × 100 ml), dried ($MgSO_4$), filtered and evaporated to give a pale yellow oil which eventually crystallized. After recrystallization from ethyl acetate hexane, a white crystalline solid was obtained, mp 125—128°C.

Example 3

Alpha-phenyl-1-(3-phenylpropyl)-4-piperidinemethanol

Step A: Phenyl [1-(3-phenylpropyl)-4-piperidinyl]-methanone hydrochloride. A solution of phenyl (4-piperidinyl)methanone (18.1 g, 0.096 mol) was dissolved in toluene (200 ml) containing 1-bromo-3-phenylpropane (21.9 g, 0.11 mol, 16.7 ml), K_2CO_3 (30.4 g 0.22 mol) and KI (0.2 g) and was refluxed for 64 h. The reaction mixture was filtered and concentrated to give a light yellow oil. This material was dissolved in toluene/EtOAc (1:1) and treated with HCl (0.096 mol) dissolved in CH_3OH/EtOAc (2:5, 35 ml) to give a precipitate which was filtered off and recrystallized twice from EtOH/Et_2O (150 ml) to give phenyl[1-(3-phenylpropyl)-4-piperidinyl]methanone hydrochloride, mp 199—200°C.

Step B: To a stirred solution of phenyl[1-(3-phenyl-propyl)-4-piperidinyl)methanone hydrochloride (6.8 g, 0.02 mol) in absolute ethanol (120 ml) was added sodium methoxide (1.08 g, 0.04 mol) followed by sodium borohydride (1.51 g, 0.04 mol. The reaction mixture was stirred for 72 h and then concentrated at reduced pressure to a solid residue. This material was stirred with aqueous 10% NaOH for 1 h and then extracted with toluene (2 × 50 ml). The extracts were washed with water and then saturated NaCl solution. The toluene solution was dried over $MgSO_4$, filtered and concentrated to a colorless oil. This material was dissolved in dry Et_2O (50 ml) and treated with a solution of HCl (0.02 mol) in CH_3OH/EtOAc (1:4, 12.5 ml. The resultant precipitate was dissolved in water, basified using 10% aqueous NaOH and extracted into toluene. The toluene solution was washed with saturated aqueous NaCl dried over $MgSO_4$, filtered and concentrated to a solid. This material was flash chromatographed on a 2.5 × 6.0 inch silica gel column, and eluted with CH_3OH/CH_2Cl_2 (1:9). The resultant fractions (7—9) eventually solidified and were recrystallized from acetone to give alpha-phenyl-1-(3-phenylpropyl)-4-piperidenemethanol, mp 87—88°C.

Example 4

Alpha-(4-methylphenyl)-1-(2-phenylethyl)-4-piperidinemethanol HCl

Step A: (4-Methylphenyl) [1-(2-phenylethyl)-4-piperidinyl]methanone HCl. A mixture containing (4-methyl-phenyl)(4-piperidinyl)methanone (10.5 g, 0.052 mol), 2-bromoethyl benzene (11.1 g, 0.06 mol, 8.2 ml) in dry DMF (125 ml) was stirred at 100°C for 23 h. The cooled reaction mixture was poured into H_2O (600 ml) and extracted with toluene (4 × 200 ml). The extracts were washed with H_2O (2 × 100 ml) and saturated aqueous NaCl (100 ml) and dried over $MgSO_4$. The mixture was filtered and the filtrate concentrated to a solid residue which was dissolved in dry Et_2O and filtered . The filtrate was treated with a solution of HCl (0.052 mol) in CH_3OH/EtOAc (9:20, 29 ml). The mixture was cooled and filtered to give a light tan powder. The solid was recrystallized twice from EtOH/Et_2O to give (4-methylphenyl)[1-(2-phenylethyl)-4-piperidinyl]methanone hydrochloride, which contains 0.4 mol of water of hydration and melts at 261—263°C.

Step B: A solution of (4-methylphenyl)[1-(2-phenyl-ethyl)-4-piperidinyl]methanone hydrochloride (9.5 g, 0.028 mol) in absolute ethanol (350 ml) was treated first by the addition of $NaOCH_3$ (1.62 g, 0.03 mol) and then, portionwise, with sodium borohydride (2.27 g, 0.06 mol) and stirred at room temperature for 18 h. The reaction mixture was concentrated to a solid and stirred with 10% aqueous NaOH. The mixture was extracted with CH_2Cl_2 (3 × 50ml). The CH_2Cl_2 solution was washed with water and then saturated NaCl solution, and dried over Na_2SO_4. After filtering off the Na_2SO_4, the filtrate was concentrated to a solid. This material was dissolved in EtOAc/Et_2O (1:1, 200 ml) and treated with a solution of HCl (0.023 mol) in CH_3OH/EtOAc (3:10, 13 ml). The resulting precipitate was twice recrystallized from butanone containing a small amount of CH_3OH to give alpha(4-methylphenyl)-1-(2-penylethyl)-4-piperidinemethanol hydrochloride, mp 181—183°C.

Example 5

Alpha-(4-methoxyphenyl)-1-(2-phenylethyl)-4-piperdinemethanol HCl

Step A: (4-Methoxyphenyl)[1-(2-phenylethyl)-4-piperidinyl]methanone HCl. A reaction mixture containing 4-(methoxyphenyl)(4-piperidinyl)methanone (10.3 g, 0.047 mol), 2-bromoethylbenzene (9.57 g, 0.052 mol, 7.1 ml) and K_2CO_3 (15.2 g, 0.11 mol) in dry DMF (100 ml) was stirred at 90°C for 65 h. The cooled reaction mixture was poured into H_20 (500 ml) and extracted with toluene (3 × 100 ml). The extracts were washed with H_20 and saturated aqueous NaCl solution and dried over $MgSO_4$. The mixture was filtered and the filtrate concentrated to a residue which was triturated with hexane and filtered. The resulting precipitate (0.022 mol) was dissolved in dry Et_20 and treated with a solution of HCl (0.022 mol) and CH_3OH/EtOAc (2:5, 14 ml) to give a precipitate which was twice recrystallized from EtOH/Et_20, to give (4-methoxyphenyl)[1-(2-phenylethyl)-4-piperidinyl]methanone hydrochloride, mp 238.5-239.5°C.

Step B: A solution of (4-methoxyphenyl)[1-(2-phenylethyl)-4-piperidinyl]methanone hydrochloride (3.5 g, 9.7 mmol) in absolute EtOH (75 ml) was treated with sodium methoxide (0.53 g, 9.7 mmol) followed by sodium borohydride (1.08 g, 20 mmol) and the mixture stirred for 42 h at room temperature. The reaction mixture was filtered and the filtrate concentrated to a solid residue which was dissolved in absolute Et_20 and treated with HCl (9.7 mmol) dissolved in CH_3OH/EtoAc (1:3, 8 ml). The resulting precipitate was filtered and recrystallized from CH_3OH/Et_20 to give alpha-(4-methoxyphenyl)-1-(2-phenylethyl)-4-piperidinemethanol hydrochloride, mp 162.5-164°C.

Example 6

Alpha-[4-(1-methylethyl)phenyl]1-(2-phenylethyl)piperidinyl]-methanol HCl.

Step A: [4-(1-methylethyl)phenyl](1-(2-phenylethyl)piperidinyl]methanone HCl. A solution of [4-(1-methylethyl)phenyl](4-piperidinyl)methanone (43 g, 0.19 mol) in toluene (500 ml) was treated with 2-bromoethylbenzene (37 g, 0.2 mol), K_2CO_3 (25 g, 0.18 mol), $KHCO_3$ (25 g, 0.25 mol) and potassium iodide (0.1 g) and the mixture heated on a steam bath for 68 h. The reaction mixture was filtered and the filtrate treated with ethereal hydrogen chloride until acid to congo red indicator paper. The resultant precipitate was filtered off and recrystallized twice from CH_3OH/butanone to give [4-(1-methylethyl)-phenyl][1-(2-phenylethyl)piperidinyl-methanone hydrochloride, mp 251-253°C. By following the sodium borohyride reduction procedure of the foregoing example there is obtained the desired product of this example.

Example 7

Alpha-(3,5-dimethylphenyl)-1-(2-phenylethyl)alpha-4-piperidinemethanol

Step A: (3,5-Dimethylphenyl)[1-(2-phenylethyl)-4-piperidinyl] methanone HCl. A solution of 5-bromo-m-xylene (22.3 g, 0.12 mol) in dry THF (50 ml) was added under N_2 to an oven dried 1 L round bottom flask containing Mg turnings (3.0 g, 0.12 mol) and a crystal of I_2 covered with dry THF (50 ml) at a rate such that the THF gently refluxed once the reaction had commenced. After the addition was complete, the mixture was stirred for 1 h at room temperature. At this time the Grignard solution was diluted to 500 ml with dry THF and 4-cyano-1-(2-phenylethyl)piperidine (15.0 g, 0.12 mol) in dry THF (50 ml) was added over a period of 15 min. Dry toluene (250 ml) was added and the mixture refluxed while THF was distilled off until a reaction temperature of 85°C was reached. The mixture was refluxed at this temperature overnight (16 h). It was then cooled in an ice bath and 1N H_2SO_4 (200 ml) was added dropwise with vigorous stirring. When the addition was complete, the mixture was warmed to room temperature and stirred an additional 3 h. The aqueous phase was separated and washed twice more with toluene (200 ml) before it was basified with aqueous 2N NaOH and extracted with Et_20 (3 × 200 ml). The extract was washed with saturated aqueous NaCl (1 × 250 ml), dried ($MgSO_4$), filtered and evaporated to give a yellow oil. This oil was distilled (Kugelrohr) to give a yellow glass which crystallized upon standing. This material was recrystallized from ether to give a white crystalline powder, mp 76-78°C.

The hydrochloride salt was prepared by adding the free base to a cold methanol solution containing one equivalent of HCl. This solution was evaporated to dryness and the residue recrystallized from methanol-butanone to give fluffy white cystals, mp 211-214°C.

Step B: To a solution of (3,5-dimethylphenyl)[1-(2-phenylethyl)-4-piperidinyl]methanone (21.5 g, 66.9 mmol) in methanol (300 ml) cooled in an ice bath was added portionwise with stirring sodium borohydride (2.53 g, 66.9 mmol). The reaction was allowed to warm to room temperature and stirred overnight (16 h). This mixture was evaporated and the residue stirred in Et_20, washed with H_20 (3 × 100 ml), saturated aqueous NaCl (1 × 100 ml), dried ($MgSO_4$), filtered and evaporated to give a light yellow solid. This solid was recrystallized from butanone to give a white crystalline solid, mp 150-154°C.

Example 8

1-(2-phenylethyl)-alpha-[3-(trifluoromethyl)phenyl]-4-piperidenemethanol

Step A: [1-(2-Phenylethyl)-4-piperidinyl][3-(trifluoromethyl)-phenyl]methanone HCl. A solution of 3-bromobenzotrifluoride (17 ml, 0.12 mol) in dry THF (50 ml) was added under N_2 to an oven dried 1 L round bottom flask containing Mg turnings (3.0 g, 0.12 mol) and a crystal of I_2 covered with dry THF (50 ml) at a rate such that the THF gently refluxed once the reaction had commenced. After the addition was complete, the mixture was stirred for 1 h at room temperature. At this time the Grignard solution was diluted to 500 ml with dry THF and 4-cyano-1-(2-phenylethyl)piperidine (15.0 g, 0.12 mol) in dry THF (50 ml) was added over a period of 15 min. Dry toluene (250 ml) was added and the mixture refluxed while THF was distilled off until a reaction temperature of 85°C was reached. The mixture was refluxed at this temperature overnight (16 h). It was then cooled in an ice bath and IN H_2SO_4 (200 ml) was added dropwise with vigorous stirring. When the addition was complete, the mixture was warmed to room temperature and stirred an additional 1 h. The aqueous phase was separated and washed twice more with toluene (200 ml) before it was basified with aqueous 2N NaOH and extracted with Et_20 (3 × 200 ml). The extract was washed with aqueous saturated NaCl (1 × 250 ml), dried ($MgSO_4$], filtered and evaporated to an orange oil. This oil was distilled (Kugelrohr) to give a yellow glass (bp 120-130°C, 1 mm Hg) which crystallized upon standing. This material was recrystallized from Et_20 to give white needles, mp 70-73°C.

The hydrochloride salt was prepared by adding a solution of free base in methanol to a cold methanol solution containing one equivalent of HCl. This solution was evaporated to dryness and the residue recrystallized from methanol/butanone to give a white crystalline solid, mp 248-251°C.

Step B: To a solution of [1-(2-phenylethyl)-4-piperidinyl][3-(trifluoromethyl)-phenyl]methanone (2.8 g, 7.75 mmol) in methanol (50 ml) cooled in an ice bath was added portionwise sodium borohydride (0.3 g, 7.75 mmol). The reaction was allowed to warm to room temperature and stirred an additional 4 h. The mixture was evaporated and the residue extracted with Et_20, washed with H_20 (3 × 100 ml), saturated aqueous NaCl (1 × 100 ml), dried (Mg SO_4), filtered and evaporated to give a white solid. This solid was recrystallized from ether/hexane to give white needles, mp 143-147°C.

Example 9

Alpha-(2,3-dimethoxyphenyl)-1-(2-phenylethyl)-4-piperidenemethanol HCl

Step A: 1-(2-Phenylethyl)piperidine-4-carboxaldehyde. To a solution of 4-cyano-1-(2-phenylethyl)-piperidine (6.5 g, 30.3 mmol) in dry toluene (100 ml) cooled in an ice bath was added dropwise 43 ml (43 mmol) of 1M diisobutylaluminum hydride in hexane. After the addition was complete, the mixture was warmed to room temperature and stirred overnight (16 h). Methanol was added to decompose any unreacted reagent and H_2O was added with vigorous stirring. The gelatinous aluminum salts were removed by filtration through Celite® and the filtrate extracted with toluene (2 × 100 ml). The extracts were combined, washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated to give a clear oil. This oil was flash chromatographed on silica gel using acetone as eluent to give product as a clear oil, which was used without further purification.

Step B: To a solution of veratrole (2.5 ml, 19.6 mmol) in dry THF (150 ml) cooled at 0°C was added 13 ml (20.7 mmol) of 1.6 M n-butyllithium dropwise. This mixture was kept at 0°C for another 5 h before it was cooled to −45°C and 1-(2-phenylethyl)piperidine-4-carboxaldehyde (3.6 g, 16.6 mmol) in dry THF (10 ml) was added dropwise. The mixture was kept at −45°C for 1 h before it was allowed to warm to room temperature and stirred overnight (16 h). The reaction mixture was poured into 5% aqueous NH_4Cl, extracted with Et_20 (3 × 100 ml), dried ($MgSO_4$), filtered and evaporated to an orange oil.

The hydrochloride salt was prepared by adding a solution of the free base in methanol to a cold methanol solution containing one equivalent of HCl. This solution was evaporated to give a foam which crystallized from a vigorously stirred acetone/hexane solution. Two recrystallizations from methanol/butanone gave pale orange crystals, mp 182-185°C.

Example 10

Alpha-(3,4-dichlorophenyl)-1-(2-phenylethyl)-4-piperidinemethanol hydrochloride

Step A: (3,4-Dichlorophenyl)[1-(2-phenylethyl)-4-piperidinyl]methanone HCl. A solution of 1-bromo-3,4-dichlorobenzene (10.0 g, 44.2 mmol) in dry THF (50 ml) was added under N_2 to an even dried 1 L round bottom flask containing Mg turnings (1.2 g, 49.4 mmol) and a crystal of I_2 covered with dry THF (50 ml) at a rate such that the THF gently refluxed once the reaction had commenced. After the addition was completed the mixture was stirred for 1 h at room temperature. At this time the Grignard solution was diluted to 500 ml with dry THF and 4-cyano-1-(2-phenylethyl)piperidine (9.5 g, 44.2 mmol) in dry THF (50 ml) was added over a period of 15 min. Dry toluene (250 ml) was added and the mixture refluxed while THF was distilled off until a reaction temperature of 80°C was reached. The mixture was refluxed at this temperature overnight (16 h). It was then cooled in an ice bath and IN H_2SO_4 (200 ml) was added dropwise with vigorous stirring. When this addition was completed, the mixture was warmed to room temperature and stirred an additional 3 h. The aqueous phase was separated and washed twice more with toluene (200 ml), basified with aqueous 2N NaOH and extracted with Et_20 (3 × 200 ml). The extract was washed with saturated aqueous NaCl (1 × 250 ml), dried ($MgSO_4$), filtered and evaporated to give an orange solid. This solid was flashed chromatographed on silica gel using 20% acetone/dichloromethane as eluent and the resultant product triturated with Et_20 to give a light orange solid.

The hydrochloride salt was prepared by adding the free base to a cold methanol solution containing one equivalent of HCl. This solution was evaporated to dryness and the residue recrystallized from methanol/butanone to give a white solid, mp 238-242°C with decomposition.

Step B: To a solution of (3,4-dichlorophenyl)[1-(2-phenylethyl)-4-piperidinyl]methanone (1.9 g, 5.2 mmol) in methanol (50 ml) cooled in an ice bath was added portionwise sodium borohydride (0.6 g, 15.9 mmol). The reaction was allowed to warm to room temperature and stirred an additional 4 h. The mixture was evaporated and the residue stirred in Et_20, washed with H_20 (3 × 100 ml), saturated aqueous NaCl (1 × 100 ml), dried ($MgSO_4$), filtered and evaporated to give a white solid.

The hydrochloride salt was prepared by adding the free base to a cold methanol solution containing one equivalent of HCl. This solution was evaporated to give a pale yellow foam which crystallized from a vigorously stirred acetone/hexane solution. Recrystallization from methanol/butanone gave a white solid, mp 161-164°C.

In a similar manner, by substantially following the teachings of the foregoing examples substituting the appropriate reactants there may be produced the following compounds.

(4-fluorophenyl)[1-(2-phenylethyl)-4-piperidinyl]methanol,
Alpha-phenyl-[-1(4-Phenylbutyl)-4-piperidinyl]methanol,
Alpha-(3,4-dimethoxyphenyl)[1-(2-Phenylethyl)-4-piperidinyl]methanol.
Alpha-phenyl[1-(4-aminophenylethyl)-4-piperidinyl methanol,
Alpha-phenyl[1-(4-methoxphenylethyl)]-4-piperidinyl methanol,
Alpha-(4-methoxyphenyl)-[1-(4-methoxyphenylethyl)]-4-piperidinyl methanol,
Alpha-(2,3-dimethoxyphenyl)-[1-(4-methoxyphenylethyl)]-4-piperidinyl methanol,
Alpha-phenyl[1-(4-methylphenylethyl)]-4-piperidinyl methanol,
Alpha-phenyl[1-(4-fluorophenylethyl)]-4-piperidinyl methanol,
Alpha-(4-hydroxyphenyl)-[1-(2-phenylethyl)]-4-piperidinyl methanol,
Alpha-(3,4-dihydroxphenyl)-[1-(2-phenylethyl)]-4-piperidinyl methanol.

The compounds of this invention have very interesting biochemical and pharmacological activities. The compounds (I) are potent and selective serotonin antagonists in that, at relatively low doses, they inhibit the binding of serotonin at the $5HT_2$ receptor sites with little, if any, inhibition of the binding of serotonin at the $5HT_1$ receptor sites. Further, since it has been reported that the receptor subserving the serotonin vasoconstriction is of the $5HT_2$ subtype, the serotonin antagonism at the $5HT_2$ receptor sites of the compounds of this invention will also be useful in the treatment of such serotonin-mediate disease states as anorexia nervosa, variant angina, Raynaud's phenomena and coronary vasospasms and in the prophylactic treatment of migraine.

Using standard laboratory *in vitro* and *in vivo* methodology, either alone or in comparison studies with known serotonin antagonists, it is readily seen that the compounds of this invention are potent serotonin antagonists at the $5HT_2$ receptor sites with virtually no activity at the $5HT_1$, adrenergic alpha-I, dopamine D-2 or muscarinic cholinergic receptors. By contrast with such well-known agents as ketanserin, methysergide and cyproheptadine such selectivity is, indeed, unique.

For example, utilizing anesthetized ganglion-blocked dogs to assess alpha-adrenergic and sertoninergic blockade, it is to be found that the compounds of this invention antagonize the effects of a serotonin challenge *in vivo* (i.e., eliminated the pressor response to serotonin) and had no effect on the phenylephrine *in vivo* challenge thus demonstrating *in vivo* antagonism of the vascular effects of serotonin which is accompanied with little, if any, alpha-adrenergic receptor blocking activity. Ketanserin on the other hand will block both.

As with both ketanserin and cyproheptadine, the compounds of this invention were effective in blocking the effects of serotonin as measured in the standard 5-hydroxytryptophan-induced "head twitch" *in vivo* (mice) laboratory model. Further, contrary to findings with ketanserin, it is to be found that compounds of this invention have no significant anti-hypertensive activity in conscious spontaneously hypertensive rats (SHR). However, in anesthetized spontaneously hypertensive rats, compounds of this invention produce a marked decrease in systolic blood pressure.

In summary, based on comparative studies it is expected that in view of their selectivity in exerting potent anti-serotonin effects, the compounds of this invention will exhibit an improved pharmacologically active profile over that exhibited by ketanserin (a compound being clinically evaluated for use in the treatment of cardiovascular diseases, e.g. hypertension, peripheral vascular disease, thrombotic episodes and cardiopulmonary emergencies) for, although a potent $5HT_2$ antagonist, it is non-selective in that it blocks H-I and alpha-I adrenergic receptors. Similarly, because of their numerous side effects the marketed serotonin antagonists methysergide and cyproheptadine have a less desirable pharmacological profile than that possessed by the compounds of this invention.

In addition, the compounds of this invention exhibit topical anesthetic activity similar in effect to that of procaine, and they also exhibit an analgesic effect in the standard acetic-acid-induced writhing test.

The compounds (I) exert their serotonin antagonist-induced pharmacological activities at 1—10 mg/kg when parenterally administered and at 0.1—3 mg/kg when intravenously administered. On comparative bases it is expected that the compounds of this will exert their end-use therapeutic effects at 30—600 mg per day (on 70 kg body weight), this amount being administered in divided doses. In each specific instance, depending on the severity and type of disease state, the attending diagnostician will readily be able to determine the dosage and its frequency of administration.

Further, the compounds of this invention also exhibit significant anti-fibrillatory effects when tested according to standard laboratory techniques, said techniques being useful in the determination of anti-arrythmic properties. Thus, the compounds, particularly alpha-phenyl-1-(2-phenylethyl)-4-piperidinemethanol (and its salts), are useful in the prevention and/or treatment of ventricular fibrillatory aberrations due to acute myocardial ischemia. Other arrhythmic conditions comtemplated include ventricular tachycardia, atrioventricular nodal beats, auricular flutter, auricular fibrillation and premature ventricular contractions.

The compounds of this invention exert their anti-arrythmic pharmacological activities at 1—100 mg/kg when parenterally administered and at 0.1—10 mg/kg when administered intravenously.

The compounds of this invention, as defined by Formula I, can be administered as such, or can be administered in the form of a composition comprising the active ingredient and any of the commonly used pharmaceutical carriers. These carriers must be compatible with the active ingredient, and can be either solid or liquid, therapeutically active or inert. By using such carriers, one can make these compositions, in the form of tablets, capsules, powders, suppositories, oral suspensions, or syrups. The compositions can also be made in the form of sterile solutions which are suitable for injection. The compositions will contain from 1% to 95% by weight of active compound, and from 5% to 99% by weight of a suitable pharmaceutical carrier. These ranges, however, are not critical and can be varied as desired according to the circumstances.

A sterile solution suitable for injection is prepared by admixing from 0.5 to 5 parts by weight of the active ingredient, preferably in the form of its salt, and from 95 to 99.5 parts by weight of water or isotonic saline solution at a temperature and for time sufficient to dissolve the active ingredient. This solution is then sterilized by filtration or by the application of heat.

These injectable solutions can be prepared with a high concentration of active ingredient. The solution is then diluted to a desired concentration before it is used.

The compounds of Formula I can also be administered in the form of hard or soft gelatin capsules. These capsules are filled with the proper amount of active ingredient and solid filler, such as starch, gelatin, lactose, talc, stearic acid, or magnesium stearate. Such a capsule can contain from 5 to 50 milligrams of active material, thus providing a minimum dose of active ingredient in a form convenient for oral administration.

The compounds of Formula I, when mixed with a suitable carrier, can also be formulated as tablets. Such carriers must be compatible with the active ingredient and can be the carriers mentioned for use with capsules, or can be such binders or fillers as cornstarch, acacia, gelatin, or cellulosic materials. Generally, any of the tableting materials conventionally used in pharmaceutical practice can be employed if there is no incompatibility with the active ingredient.

The tablets are made by admixing the active ingredient, a suitable filler, a lubricant or mold-release agent, and a binder, and compressing the mixture in a conventional tableting machine into tablets of a preselected size. Preferably, each tablet will contain from 5 to 50 milligrams of active ingredient. The tablet can be scored so that they are easily broken. Optionally, the tablets can be coated with tablet-coating materials in order to make them more attractive and palatable. They can also have enteric coatings so that they will release their ingredients slowly and over a longer period.

The pharmaceutical carrier in such suspensions or syrups can be an aqueous vehicle such as an aromatic water, a syrup, or a pharmaceutical mucilage. Suitable aromatic waters include the following: Anise Water, N.F. (IX); Bitter Almond Water, N.F. (VIII); Camphor Water, N.F.; Cinnamon Water, U.S.P.; Fennel Water, N.F.; Peppermint Water, U.S.P.; Spearmint Water, N.F. (IX); Wintergreen Water, N.F. (IX). Suitable syrups include the following: Syrup (Simple Syrup), U.S.P.; Acacia Syrup, U.S.P.; Aromatic Eriodictyon Syrup, N.F.; Aromatic Rhubarb Syrup, N.F. (IX); Cacao Syrup, U.S.P.; Cherry Syrup, U.S.P.; Cinnamon Syrup, N.F. (IX); Citric Acid Syrup, U.S.P.; Compound Sarsparilla Syrup, N.F.; Compound White Pine Syrup, N.F.; Ginger Syrup, N.F. (IX); Glycyrrhiza (Licorice) Syrup, U.S.P.; Orange Syrup, U.S.P.; Orange Flower Syrup, N.F.; Raspberry Syrup, U.S.P.; Rhubard Syrup, N.F.(IX); Tolu Balsam Syrup, U.S.P.; Wild Cherry Syrup, U.S.P. Suitable pharmaceutical mucilages include the following: Acacia (Gum Arabic), U.S.P.; Acacia Mucilage, U.S.P.; Tragacanth, U.S.P.; Tragacanth Mucilage, N.F. The pharmaceutical carrier in the suspensions or syrups can also be a hydroalcoholic vehicle, such as an elixir. Suitable elixirs include the following: Aromatic Elixir, U.S.P.; Red Aromatic Elixir, N.F.; Glycyrrhiza Elixir, N.F.; Iso-Alcoholic Elixir (Iso-Elixir), N.F. Coloring agents, tinctures, spirits and other adjuvants can be admixed with the composition if desired.

Typical formulations incorporating the compounds of Formula I are described below. These formulations are intended to be illustrative merely, and no limitation is implied or intended.

Tablet Formulation

Formula	Grams per 1000 tablets
Active Ingredient*	20.0
Lactose	270.0
Dicalcium phosphate, hydrous	122.5
Polyvinylpyrrolidone	25.0
Polyvinylglycol 1500	7.5
Corn starch	50.0
Magnesium stearate	5.0
	500.0

*Title compound of example 1

Mix the active ingredient, the lactose and the dicalcium phosphate. Dissolve the polyethylene glycol 1500 and the polyvinylpyrrolidone in approximately 20 ml of water. Granulate the powder blend with the water solution, adding additional water if necessary, to produce a damp mass. Pass the wet granulation through a 12 mesh screen; spread on trays and air dry at 35°C. Blend the dry granules with the starch and the magnesium stearate. Compress into 500 mg tablets.

Capsule Formulation

Formula	Grams per 1000 capsules
Active Ingredient*	20.0
Lactose	378.0
Magnesium stearate	2.0
	400.0

*Title compound of example 1

Blend the ingredients and fill into hard gelatin capsules.

Elixir Formulation

Formula	Grams per 1000 millilitres
Active Ingredient*	40.0
Sugar	do 500.0
Glycerin	do 200.0
Compound orange spirit	ml 10.0
Alcohol	ml 100.0
Amaranth	ml 0.1
Water, q.s. 1000.0 ml.	

*Title compound of example 1

Dissolve the active ingredient, the sugar, the glycerin and the amaranth successively in approximately 400 ml of water with the aid of heat. Cool the solution to room temperature. Dissolve the compound orange spirit in the alcohol and add the alcoholic solution to the elixir base. Add sufficient water to make the product measure 1000 ml and agitated until homogeneous. Clarify the elixir by passing it through an asbestos pad, using a filter aid if necessary.

Injection Formulation

Formula	Grams per 1000 ampuls
Active Ingredient*	110.0
Water for injection, q.s. 1100.0 ml.	

*Title compound of example 1

Dissolve the active ingredient in the water for injection. Pass the solution through a sterile 0.45 micron membrance filter. Fill acceptically into ampuls (1.1 ml per ampul). Autoclave the sealed ampuls for 30 minutes under 20 p.s.i.g. stream pressure.

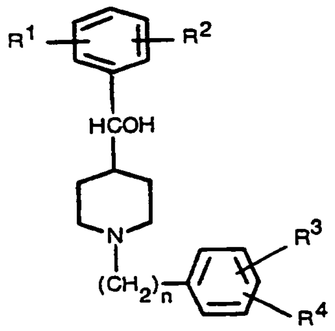
In order to achieve a satisfactory response, usually no more than 1 to 3 tablets or capsules as described above need be administered daily. The elixir described is usually administered in the amount of 1 to 3 teaspoons (5 cc.) per day while the usual injection dosage is 1 to 3 cc. per day. In severe or aggravated conditions, additional medicine may be administered.

As is true for most classes of compounds useful as therapeutic agents not all members have the same biological profile. In the present instance, on the basis of *in vitro* and *in vivo* studies, particularly when compared with prior art compounds, it is to be that when those compounds of Formula I wherein n is 2 such compounds are most preferred. When the R and R^1 groups of the phenalkyl moiety attached directly to the nitrogen atom of the piperidinal moiety are hydrogen and such compounds are preferred. Preferred substituents on the other phenyl moiety are 4-methoxy, 4-methyl, 3-trifluomethyl, 3,4-dichloro, 3,4-dimethoxy, 3,5-dimethyl and most preferred is when all R groups are hydrogen. Preferred specific compounds are:

alpha-phenyl-1-(2-phenylethyl)-4-piperidine methanol,
alpha-phenyl-1-(3-phenylpropyl)-4-piperidine methanol,
alpha-(4-methylphenyl)-1-(2-phenylethyl)-4-piperidine methanol,
alpha-(4-methoxyphenyl)-1-(2-phenylethyl)-4-piperidine methanol,
alpha-(3,5 dimethylphenyl)-1-(2-phenylethyl)-4-piperidine methanol,
alpha-(3-(trifluoromethyl)phenyl)-1-(2-phenylethyl)-4-piperidine methanol,
alpha-(2,3-dimethoxyphenyl)-1-(2-phenylethyl)-4-piperidine methanol, the first and last named compounds being most preferred.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the general formula (I),

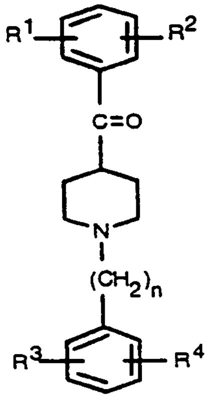


(I)

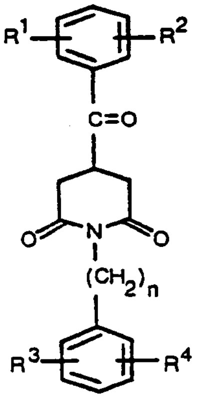
the optical isomers thereof and the pharmaceutically acceptable salts thereof wherein n is 2, 3 or 4, each of R^1, R^2, R^3, R^4 independently is hydrogen, halogen, trifluormethyl, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or amino.

2. A compound of claim 1 wherein n is 2.
3. A compound of claim 1 wherein n is 3.
4. A compound of claim 1 wherein R^3 and R^4 are hydrogen.
5. A compound of claim 4 wherein R^1 and R^2 are hydrogen.
6. A compound of claim 1 wherein R^1 and R^2 are methoxy and R^3 and R^4 are hydrogen.
7. A compound of claim 1 wherein R^1 is methoxy and each of R^2, R^3 and R^4 is hydrogen.
8. A compound of claim 1 wherein R^1 and R^2 are halogen and R^3 and R^4 is hydrogen.
9. A compound of claim 1 wherein R is methyl and R^2, R^3, R^4 are hydrogen.
10. The process for preparing a compound of the general formula (I) according to claim 1 which comprises

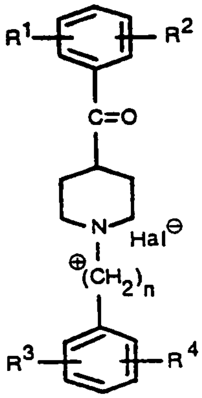
A) the chemical reduction of a compound of the formula



IIa

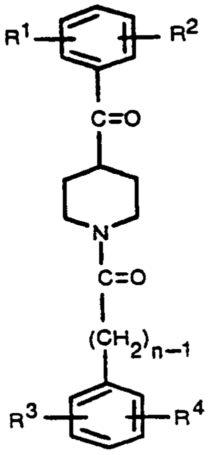


IIb



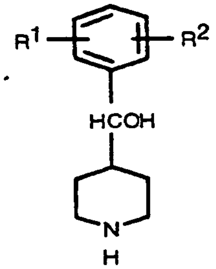
IIc

or



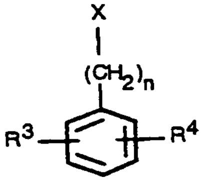
IId

B) the alkylation of a compound of the formula



III

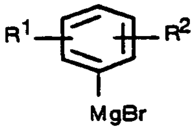
with a reactive derivative having the formula



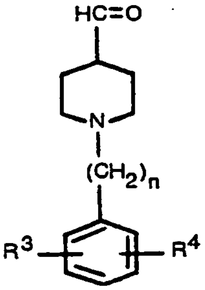
IV

wherein X is a reactive moiety, preferably a halide, tosylate, mesylate or a functional equivalent thereof, or

C) the reaction of a Grignard reagent V with an aldehyde of the formula VI



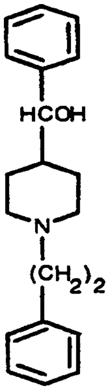
V



VI

and hydrolyzing the reaction product,
wherein R^1 to R^4 and n are defined as in claim 1.

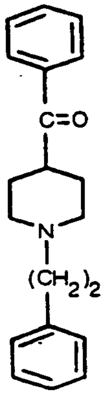
11. The process for preparing a compound of formula



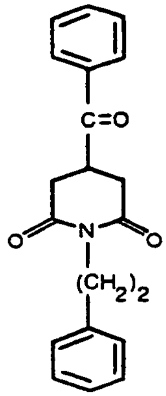
VII

which comprises

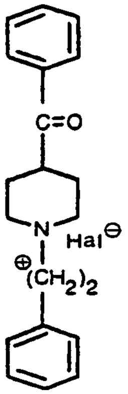
A) the chemical reduction of a compound of the formulae



VIIIa

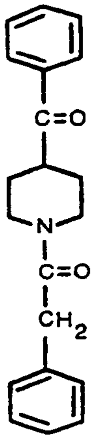


VIIIb



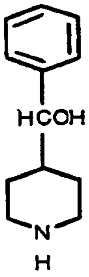
VIIIc

or



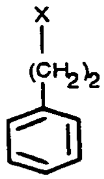
VIIId

B) the alkylation of the compound of formula IX



IX

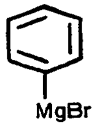
with an alkylating agent of the formula X



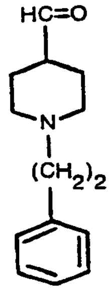
X

wherein the X-substituent is a halide, tosylate, mesylate or a functional equivalent thereof, and

C) the reaction of a Grignard reagent XI with an aldehyde of the formulae XII



XI



XII

and hydrolyzing the reaction product.

12. A compound of the general formula I according to any of claims 1 to 9 for use as a therapeutical agent.

13. A compound of the general formula I according to any of claims 1 to 9 for use in prophylactically treating migraine.

14. A compound of the general formula I according to any of claims 1 to 9 for use in treating Raynaud's phenomenon.

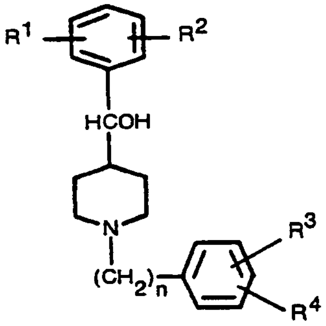
15. A compound of the general formula I according to any of claims 1 to 9 for use in treating variant angina.

16. A compound of the general formula I according to any of claims 1 to 9 for use in treating cardiac arrhythmias.

17. Pharmaceutical composition comprising a compound of the general formula I according to any of claims 1 to 9 and usual carriers and/or additives.

Claims for the Contracting State: AT

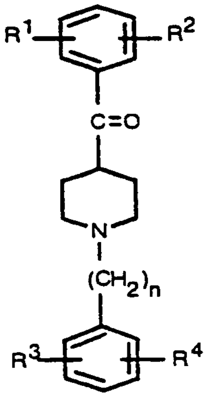
1. A process for preparing a compound of the general formula (I),



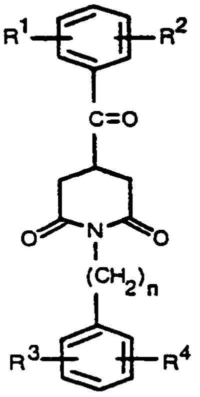
(I)

the optical isomers thereof and the pharmaceutically acceptable salts thereof wherein n is 2, 3 or 4, each of R^1, R^2, R^3, R^4 independently is hydrogen, halogen, trifluormethyl, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or amino, which comprises

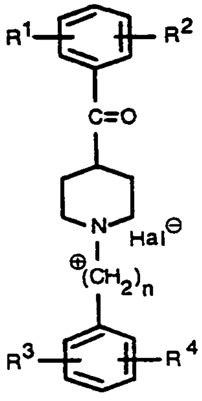
A) the chemical reduction of a compound of the formula



IIa

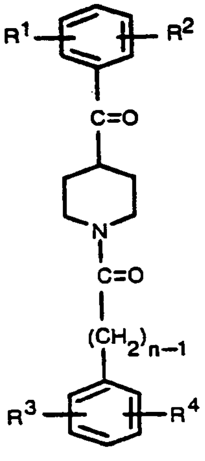


IIb



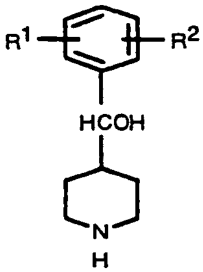
IIc

or



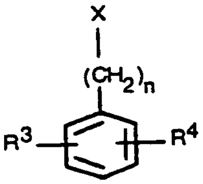
IId

B) the alkylation of a compound of the formula



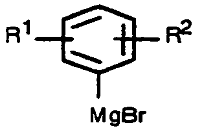
III

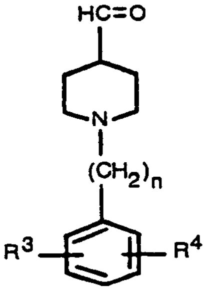
with a reactive derivative having the formula


IV

wherein X is a reactive moiety, preferably a halide, tosylate, mesylate or a functional equivalent thereof, or

C) the reaction of a Grignard reagent V with an aldehyde of the formula VI


V


VI

and hydrolyzing the reaction product.

2. The process of claim 1 for the preparation of a compound of the general formula (I) wherein n is 2.

3. The process of claim 1 for the preparation of a compound of the general formula (I) wherein n is 3.

4. The process of claim 1 for the preparation of a compound of the general formula (I) wherein R^3 and R^4 are hydrogen.

5. The process of claim 4 for the preparation of a compound of the general formula (I) wherein R^1 and R^2 are hydrogen.

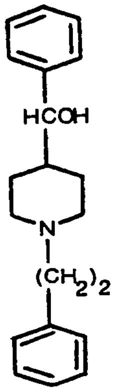
6. The process of claim 1 for the preparation of a compound of the general formula (I) wherein R^1 and R^2 are methoxy and R^3 and R^4 are hydrogen.

7. The process of claim 1 for the preparation of a compound of the general formula (I) wherein R^1 is methoxy and each of R^2, R^3 and R^4 is hydrogen.

8. The process of claim 1 for the preparation of a compound of the general formula (I) wherein R^1 and R^2 are halogen and R^3 and R^4 is hydrogen.

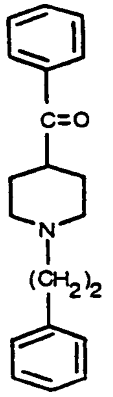
9. The process of claim 1 for the preparation of a compound of the general formula (I) wherein R is methyl and R^2, R^3, R^4 are hydrogen.

10. The process for preparing a compound of formula

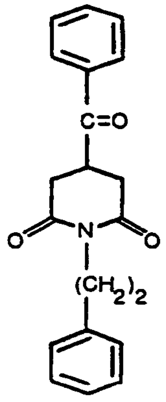

VII

which comprises

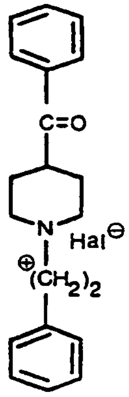
A) the chemical reduction of a compound of the formulae



VIIIa

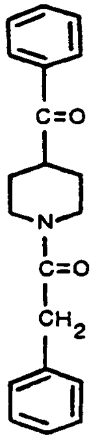


VIIIb



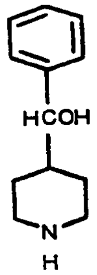
VIIIc

or



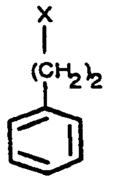
VIIId

B) the alkylation of the compound of formula IX



IX

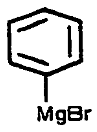
with an alkylating agent of the formula X



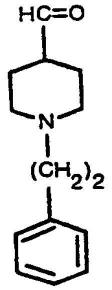
X

wherein the X-substituent is a halide, tosylate, mesylate or a functional equivalent thereof, or

C) the reaction of a Grignard reagent XI with an aldehyde of the formulae XII



XI



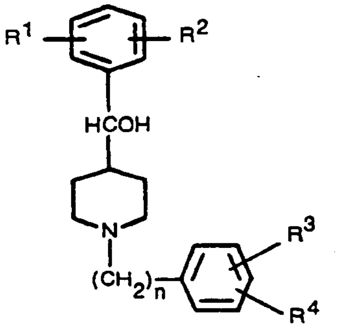
XII

and hydrolyzing the reaction product.

11. A process for preparing a pharmaceutical composition for prophylactically treating migraine, treating Raynaud's phenomenon, variant angina or cardiac arrhythmias comprising combining a compound of the general formula I obtained according to any of claims 1 to 10 and usual carriers and/or additives.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Eine Verbindung der allgemeinen Formel (I),



(I)

ihre optischen Isomere und ihre pharmazeutisch verträglichen Salze, in der n 2, 3 oder 4 ist und jeder der Reste R^1, R^2, R^3 und R^4 unabhängig voneinander ein Wasserstoff- oder Halogenatom, eine Trifluormethyl-, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, Hydroxy- oder Aminogruppe bedeutet.

2. Verbindung nach Anspruch 1, in der n 2 ist.

3. Verbindung nach Anspruch 1, in der n 3 ist.

4. Verbindung nach Anspruch 1, in der R^3 und R^4 Wasserstoffatome sind.

5. Verbindung nach Anspruch 4, in der R^1 und R^2 Wasserstoffatome sind.

6. Verbindung nach Anspruch 1, in der R^1 und R^2 Methoxygruppen und R^3 und R^4 Wasserstoffatome sind.

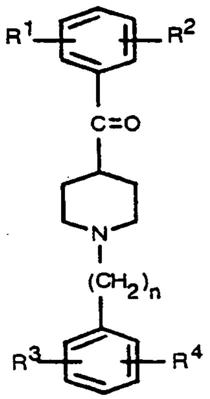
7. Verbindung nach Anspruch 1, in der R^1 eine Methoxygruppe und jeder der Reste R^2, R^3 und R^4 ein Wasserstoffatom ist.

8. Verbindung nach Anspruch 1, in der R^1 und R^2 Halogenatome und R^3 und R^4 Wasserstoffatome sind.

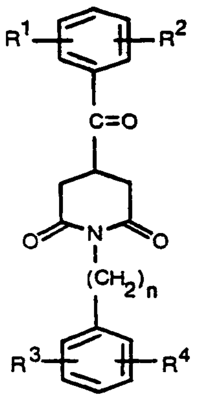
9. Verbindung nach Anspruch 1, in der R eine Methylgruppe und R^2, R^3 und R^4 Wasserstoffatome sind.

10. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (I) nach Anspruch 1, welches umfaßt:

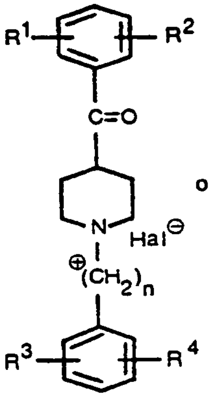
A) chemische Reduktion einer Verbindung der Formel



IIa

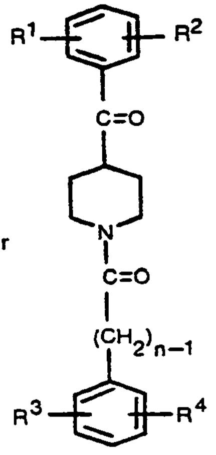


IIb



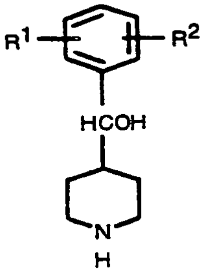
IIc

oder



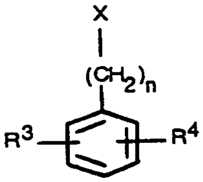
IId

B) Alkylierung einer Verbindung der Formel



III

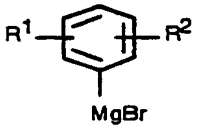
mit einem reaktiven Derivat der Formel



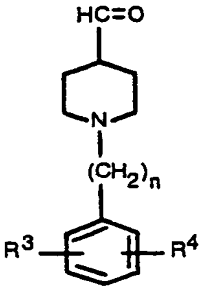
IV

in der X eine reaktive Einheit, vorzugsweise ein Halogenid, Tosylat, Mesylat oder ein funktionelles Äquivalent davon ist, oder

C) Umsetzung eines Grignard-Reagens V mit einem Aldehyd der Formel VI



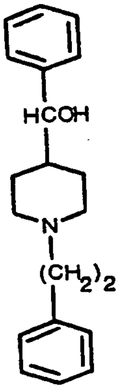
V



VI

und Hydrolyse des Reaktionsproduktes, wobei R^1 bis R^4 und n wie in Anspruch 1 definiert sind.

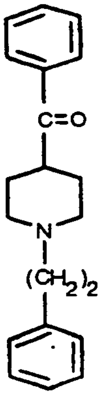
11. Verfahren zur Herstellung einer Verbindung der Formel



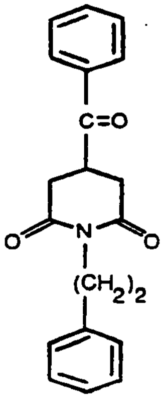
VII

welches umfaßt:

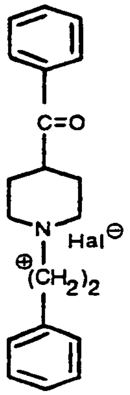
A) chemische Reduktion einer Verbindung der Formeln



VIIIa

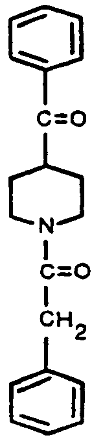


VIIIb



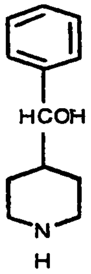
VIIIc

oder



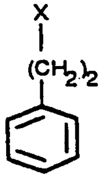
VIIId

B) Alkylierung der Verbindung der Formel IX



IX

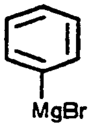
mit einem Alkylierungsmittel der Formel X



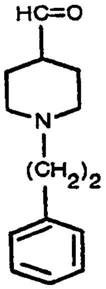
X

in der der X-Substituent ein Halogenid, Tosylat, Mesylat oder ein funktionelles Äquivalent davon ist, oder

C) Umsetzung eines Grignard-Reagens XI mit einem Aldehyd der Formel XII



XI



XII

und Hydrolyse des Reaktionsproduktes.

12. Eine Verbindung der allgemeinen Formel I nach einem der Ansprüche 1 bis 9 zur Verwendung als Arzneistoff.

13. Eine Verbindung der allgemeinen Formel I nach einem der Ansprüche 1 bis 9 zur Verwendung bei der vorbeugenden Behandlung von Migräne.

14. Eine Verbindung der allgemeinen Formel I nach einem der Ansprüche 1 bis 9 zur Verwendung bei der Behandlung des Raynaud-Phänomens.

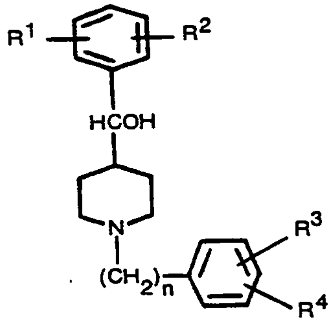
15. Eine Verbindung der allgemeinen Formel I nach einem der Ansprüche 1 bis 9 zur Verwendung bei der Behandlung von Angina-Abarten.

16. Eine Verbindung der allgemeinen Formel I nach einem der Ansprüche 1 bis 9 zur Verwendung bei der Behandlung von Herzarrhythmien.

17. Arzneimittel, umfassend eine Verbindung der allgemeinen Formel I nach einem der Ansprüche 1 bis 9 und übliche Träger- und/oder Zusatzstoffe.

Patentansprüche für den Vertragsstaat: AT

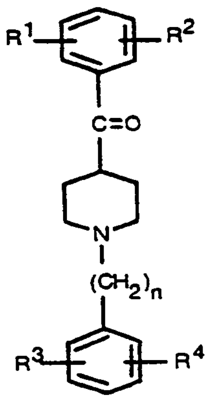
1. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (I),



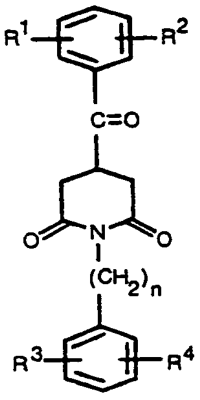
(I)

ihre optischen Isomere und ihre pharmazeutisch verträglichen Salze, in der n 2, 3 oder 4 ist und jeder der Reste R^1, R^2, R^3 und R^4 unabhängig voneinander ein Wasserstoff- oder Halogenatom, eine Trifluormethyl-, C_{1-6}-Alkyl-, C_{1-6}-Alkoxy-, Hydroxy- oder Aminogruppe bedeutet, welches umfaßt:

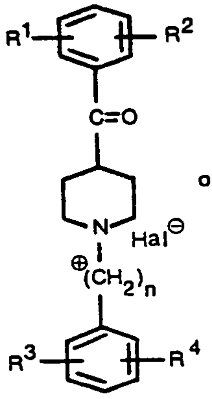
A) chemische Reduktion einer Verbindung der Formel



IIa

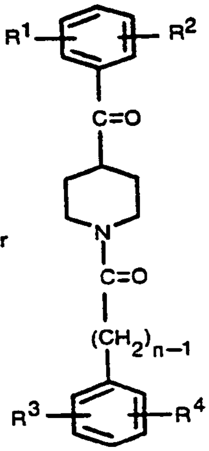


IIb



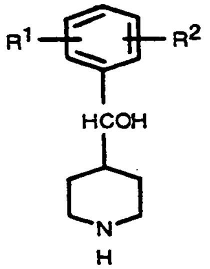
IIc

oder



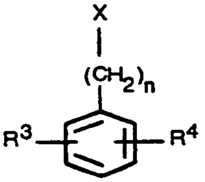
IId

B) Alkylierung einer Verbindung der Formel



III

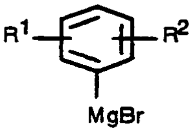
mit einem reaktiven Derivat der Formel



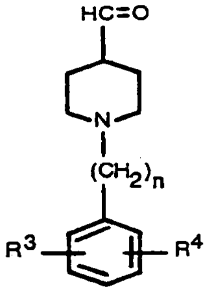
IV

in der X eine reaktive Einheit, vorzugsweise ein Halogenid, Tosylat, Mesylat oder ein funktionelles Äquivalent davon ist, oder

C) Umsetzung eines Grignard-Reagens V mit einem Aldehyd der Formel VI



V



VI

und Hydrolyse des Reaktionsproduktes.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der allgemeinen Formel (I), in der n 2 ist.

3. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der allgemeinen Formel (I), in der n 3 ist.

4. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der allgemeinen Formel (I), in der R^3 und R^4 Wasserstoffatome sind.

5. Verfahren nach Anspruch 4 zur Herstellung einer Verbindung der allgemeinen Formel (I), in der R^1 und R^2 Wasserstoffatome sind.

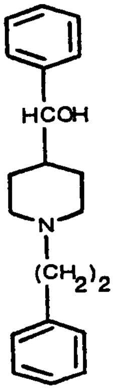
6. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der allgemeinen Formel (I), in der R^1 und R^2 Methoxygruppen und R^3 und R^4 Wasserstoffatome sind.

7. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der allgemeinen Formel (I), in der R^1 eine Methoxygruppe und jeder der Reste R^2, R^3 und R^4 ein Wasserstoffatom ist.

8. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der allgemeinen Formel (I), in der R^1 und R^2 Halogenatome und R^3 und R^4 Wasserstoffatome sind.

9. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der allgemeinen Formel (I), in der R eine Methylgruppe und R^2, R^3 und R^4 Wasserstoffatome sind.

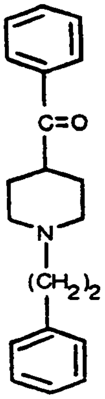
10. Verfahren zur Herstellung einer Verbindung der Formel



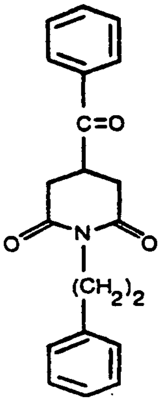
VII

welches umfaßt:

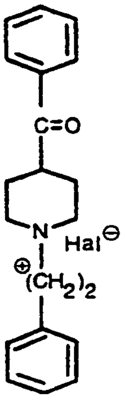
A) chemische Reduktion einer Verbindung der Formeln



VIIIa

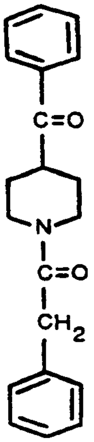


VIIIb



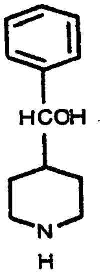
VIIIc

oder



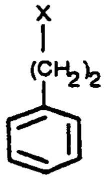
VIIId

B) Alkylierung der Verbindung der Formel IX



IX

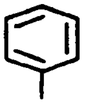
mit einem Alkylierungsmittel der Formel X



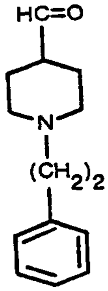
X

in der der X-Substituent ein Halogenid, Tosylat, Mesylat oder ein funktionelles Äquivalent davon ist, oder

C) Umsetzung eines Grignard-Reagens XI mit einem Aldehyd der Formel XII



XI



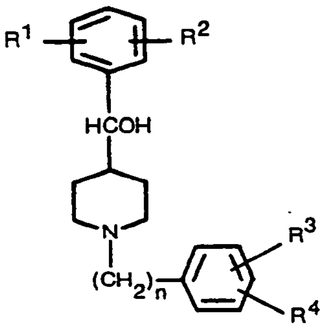
XII

und Hydrolyse der Reaktionsproduktes.

11. Verfahren zur Herstellung eines Arzneimittels zur vorbeugenden Behandlung von Migräne, Behandlung des Raynaud-Phänomens, von Angina-Abarten oder von Herzarrhythmien, umfassend das Zusammenbringen einer Verbindung der allgemeinen Formel I, erhalten nach einem der Ansprüche 1 bis 10 und üblicher Träger- und/oder Zusatzstoffe.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Un composé de formule générale (I),



(I)

ses isomères optiques et ses sels pharmaceutiquement acceptables, formule dans laquelle n est égal à 2, 3 ou 4, chacun des substituants R^1, R^2, R^3, R^4 désigne indépendamment un atome d'hydrogène, d'halogène, un groupe trifluorométhyle, C_{1-6} alkyle, C_{1-6} alcoxy, hydroxy ou amino.

2. Un composé selon la revendication 1, selon lequel n est égal à 2.

3. Un composé selon la revendication 1, selon lequel n est égal à 3.

4. Un composé selon la revendication 1, selon lequel R^3 et R^4 sont des atomes d'hydrogène.

5. Un composé selon la revendication 4, selon lequel R^1 et R^2 sont des atomes d'hydrogène.

6. Un composé selon la revendication 1, selon lequel R^1 et R^2 sont des groupes méthoxy et R^3 et R^4 sont des atomes d'hydrogène.

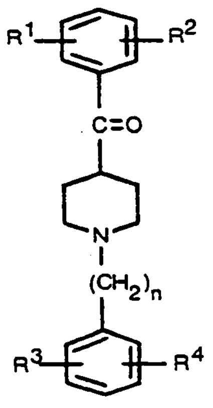
7. Un composé selon la revendication 1, selon lequel R^1 est un groupe méthoxy et chacun des substituants R^2, R^3 et R^4 est un atome d'hydrogène.

8. Un composé selon la revendication 1, selon lequel R^1 et R^2 sont des atomes d'halogène et R^3 et R^4 sont des atomes d'hydrogène.

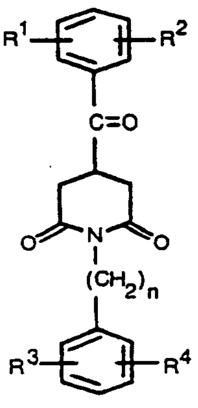
9. Un composé selon la revendication 1, selon lequel R est un groupe méthyle et R^2, R^3 et R^4 sont des atomes d'hydrogène.

10. Le procédé de préparation d'un composé de formule générale (I), selon la revendication 1 qui comprend:

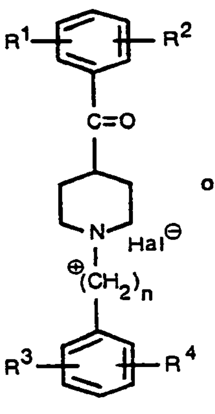
A) la réduction chimique d'un composé de formule



IIa

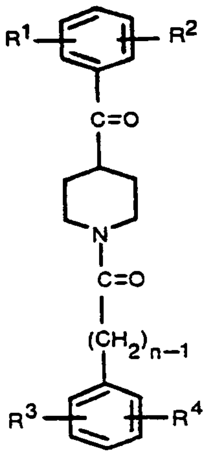


IIb



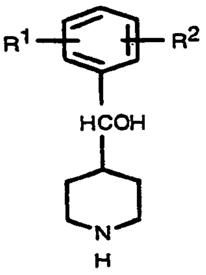
IIc

ou



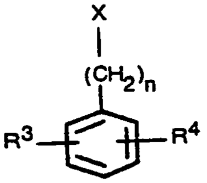
IId

B) l'alkylation d'un composé de formule



III

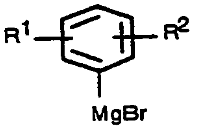
avec un dérivé réactif ayant la formule



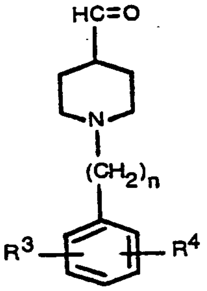
IV

dans laquelle X est une moitié réactive, de préférence un halogénure, un tosylate, un mésylate ou un équivalent fonctionnel de ceci, ou

C) la réaction d'un réactif de Grignard V avec un aldéhyde de formule (VI)



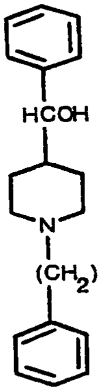
V



VI

et l'hydrolyse du produit réactionnel, formule dans laquelle R^1 à R^4 et n sont définis comme dans la revendication 1.

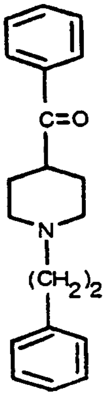
11. Le procédé de préparation d'un composé de formule



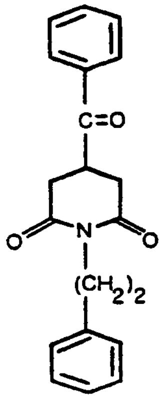
VII

qui comprend

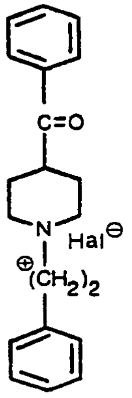
A) la réduction chimique d'un composé de formule



VIIIa

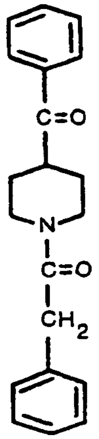


VIIIb



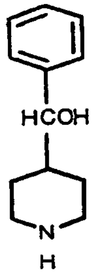
VIIIc

ou



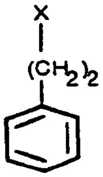
VIIId

B) l'alkylation du composé de formule (IX)



IX

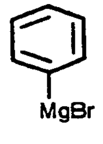
avec un agent d'alkylation de formule (X)



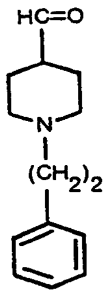
X

dans laquelle le substituant X est un halogénure, un tosylate, un mésylate ou un équivalent fonctionnel de ceci, ou bien

C) la réaction d'un réactif de Grignard XI avec un aldéhyde de formule (XII)



XI



XII

et l'hydrolyse du produit réactionnel.

12. Un composé de formule générale (I) selon l'une quelconque des revendications 1 à 9 à utiliser comme agent thérapeutique.

13. Un composé de formule générale (I) selon l'une quelconque des revendications 1 à 9 à utiliser dans

le traitement prophylactique de la migraine.

14. Un composé de formule générale (I) selon l'une quelconque des revendications 1 à 9 à utiliser dans le traitement du syndrome de Raynaud.

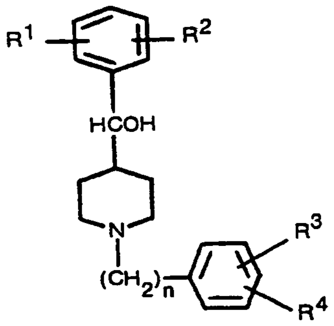
15. Un composé de formule générale (I) selon l'une quelconque des revendications 1 à 9 à utiliser dans le traitement des différentes angines.

16. Un composé de formule générale (I) selon l'une quelconque des revendications 1 à 9 à utiliser dans le traitement des arythmies cardiaques.

17. Composition pharmaceutique comprenant un composé de formule générale (I) selon l'une quelconque des revendications 1 à 9 et des véhicules et/ou des additifs habituels.

Revendications pour l'Etat contractant: AT

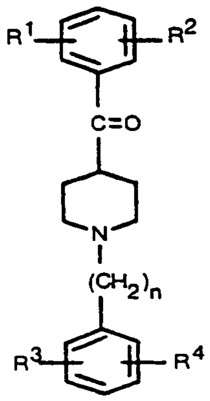
1. Un procédé de préparation d'un composé de formule générale (I)



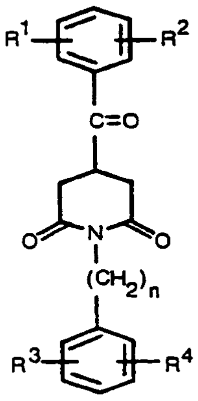
(I)

de ses isomères optiques et de ses sels pharmaceutiquement acceptables, formule dans laquelle n est égal à 2, 3 ou 4, chacun des substituants R^1, R^2, R^3, R^4 désigne indépendamment un atome d'hydrogène, d'halogène, un groupe trifluorométhyle, C_{1-6} alkyle, C_{1-6} alcoxy, hydroxy ou amino, ledit procédé comprenant:

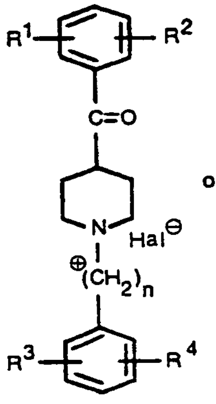
A) la réduction chimique d'un composé de formule



IIa

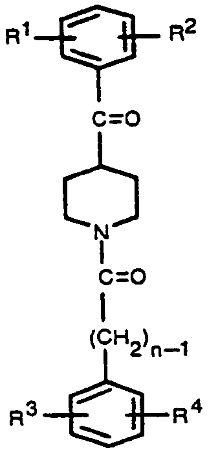


IIb



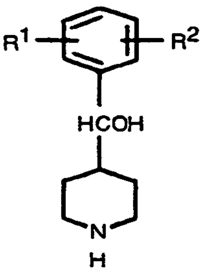
IIc

ou



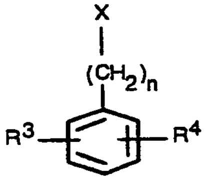
IId

B) l'alkylation d'un composé de formule



III

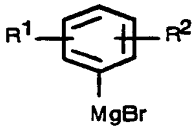
avec un dérivé réactif ayant la formule suivante



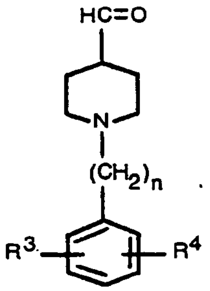
IV

dans laquelle X est une moitié réactive, de préférence un halogénure, un tosylate, un mésylate ou un équivalent fonctionnel de ceci, ou bien

C) la réaction d'un réactif de Grignard V avec un aldéhyde de formule (VI)



V



VI

et l'hydrolyse du produit réactionnel.

2. Le procédé selon la revendication 1 pour la préparation d'un composé de formule générale (I), selon lequel n est égal à 2.

3. Le procédé selon la revendication 1 pour la préparation d'un composé de formule générale (I), selon lequel n est égal à 3.

4. Le procédé selon la revendication 1 pour la préparation d'un composé de formule générale (I), selon lequel R^3 et R^4 sont des atomes d'hydrogène.

5. Le procédé selon la revendication 4 pour la préparation d'un composé de formule générale (I), selon lequel R^1 et R^2 sont des atomes d'hydrogène.

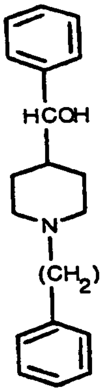
6. Le procédé selon la revendication 1 pour la préparation d'un composé de formule générale (I), selon lequel R^1 et R^2 sont des groupes méthoxy et R^3 et R^4 sont des atomes d'hydrogène.

7. Le procédé selon la revendication 1 pour la préparation d'un composé de formule générale (I), selon lequel R^1 est un groupe méthoxy et chacun des substituants R^2, R^3 et R^4 étant un atome d'hydrogène.

8. Le procédé selon la revendication 1 pour la préparation d'un composé de formule générale (I), selon lequel R^1 et R^2 sont des atomes d'halogène et R^3 et R^4 sont des atomes d'hydrogène.

9. Le procédé selon la revendication 1 pour la préparation d'un composé de formule générale (I), selon lequel R est un groupe méthyle et R^2, R^3 et R^4 sont des atomes d'hydrogène.

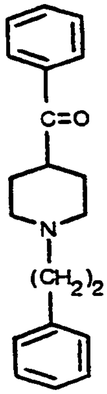
10. Le procédé de préparation d'un composé de formule



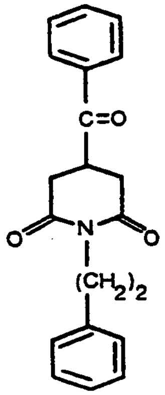
VII

qui comprend:

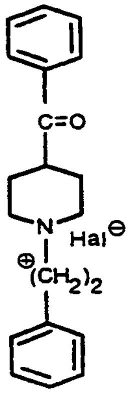
A) la réduction chimique d'un composé de formule



VIIIa

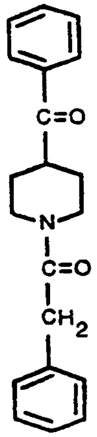


VIIIb



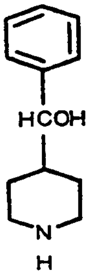
VIIIc

ou



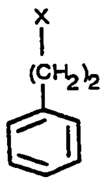
VIIId

B) l'alkylation du composé de formule (IX)



IX

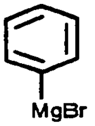
avec un agent d'alkylation de formule (X)



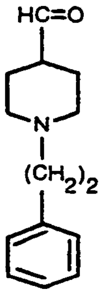
X

dans laquelle le substituant X est un halogénure, un tosylate, un mésylate ou un équivalent fonctionnel de ceci, ou bien

C) la réaction d'un réactif de Grignard (XI) avec un aldéhyde de formule (XII)



XI



XII

et l'hydrolyse du produit réactionnel.

11. Un procédé de préparation d'une composition pharmaceutique pour le traitement prophylactique de la migraine, pour le traitement du syndrome de Raynaud, des différentes angines ou des arythmies cardiaques, ledit procédé consistant à combiner un composé de formule générale (I) obtenu conformément à l'une quelconque des revendications 1 à 10 avec des véhicules et/ou des additifs habituels.